## **WEST Search History**

DATE: Thursday, December 12, 2002

Set Name side by side

| Query | Hit Count | Set Name | result set |

DB=USPT,PGPB,JPAB,EPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ

L1 mucociliary clearance and (kunitz or bikunin or aprotinin) 9 L1

END OF SEARCH HISTORY

## WEST

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### Search Results - Record(s) 1 through 9 of 9 returned.

1. Document ID: US 20020086020 A1

L1: Entry 1 of 9

File: PGPB

Jul 4, 2002

PGPUB-DOCUMENT-NUMBER: 20020086020

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020086020 A1

TITLE: Method for improving the half-life of soluble viral receptors on mucosal membranes

PUBLICATION-DATE: July 4, 2002

INVENTOR-INFORMATION:

NAME

CITY

STATE

COUNTRY

RULE-47

Lee, Peter P.

Menlo Park

CA

US

US-CL-CURRENT: 424/147.1; 424/133.1, 424/134.1, 424/135.1, 424/136.1, 424/141.1, 424/148.1, 424/149.1, 424/150.1, 424/159.1, 424/160.1, 424/161.1, 424/161.1, 424/165.1, 530/350

Full little Unation	Front   Review   Classific.	ation   vate   Keterence	Sequences Attachments	Claims KWWC	Draw Desc Image

2. Document ID: US 20020010318 A1

L1: Entry 2 of 9

File: PGPB

Jan 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020010318

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020010318 A1

TITLE: Secretory leukocyte protease inhibitor dry powder pharmaceutical compositions

PUBLICATION-DATE: January 24, 2002

INVENTOR - INFORMATION:

NAME

CITY

STATE

COUNTRY RULE-47

Niven, Ralph W.

Redwood City

CA

US

Wright, Clifford D.

Boulder

CO

US

Chang, Byeong S.

Thousand Oaks

CA

US

US-CL-CURRENT: 530/350; 435/183

Full Title Citation Front Review Classification Date Reference Sequences Attachments Claims KWC Draw Desc Image

3. Document ID: US 20010006939 A1

L1: Entry 3 of 9

File: PGPB

Jul 5, 2001

PGPUB-DOCUMENT-NUMBER: 20010006939 PGPUB-FILING-TYPE: new-utility

DOCUMENT-IDENTIFIER: US 20010006939 A1

'TITLE: SECRETORY LEUKOCYTE PROTEASE INHIBITOR DRY POWDER PHARMACEUTICAL COMPOSITIONS

PUBLICATION-DATE: July 5, 2001

INVENTOR-INFORMATION:

NAME CITY STATE COUNTRY RULE-47

NIVEN, RALPH W. REDWOOD CITY CA US WRIGHT, CLIFFORD D. BOULDER CO US CHANG, BYEONG S. THOUSAND OAKS CA US

US-CL-CURRENT: 514/2; 435/69.1, 514/44

Full Title Citation Front Review C	lassification Date Reference Sequences Attachments	Claims KWAC Draw Desc Image
X		
4. Document ID: US 6365	5156 B1	
L1: Entry 4 of 9	File: USPT	Apr 2, 2002

US-PAT-NO: 6365156

DOCUMENT-IDENTIFIER: US 6365156 B1

TITLE: Method for improving the half-life of soluble viral-specific ligands on mucosal

membranes

DATE-ISSUED: April 2, 2002

INVENTOR-INFORMATION:

NAME CITY STATE ZIP CODE COUNTRY

Lee; Peter P. Palo Alto CA

US-CL-CURRENT: 424/147.1; 424/159.1, 424/163.1, 424/164.1, 424/196.11

#### ABSTRACT:

This invention relates to methods of increasing the half-life of a viral-specific ligand on a mucosal membrane by modifying the viral-specific ligand to bind the bacteria colonized on the mucosal membrane. The invention also provides a chimeric molecule comprising a viral-specific ligand and a bacterial-specific ligand.

19 Claims, 2 Drawing figures Exemplary Claim Number: 1 Number of Drawing Sheets: 1

Full Title Citation Front Review Classification	Date Reference Sequences At	tachments Claims KVMC Draw Desc Image
5. Document ID: US 5693608 A		
L1: Entry 5 of 9	File: USPT	Dec 2, 1997

US-PAT-NO: 5693608

DOCUMENT-IDENTIFIER: US 5693608 A

TITLE: Method of administering a biologically active substance

DATE-ISSUED: December 2, 1997

INVENTOR-INFORMATION:

#### Record List Display

http://westbrs:8002/bin/gate.exe?f=TOC&s...dbname=USPT,PGPB,JPAB,EPAB,DWPI&ESNAME=-

NAME CITY STATE ZIP CODE COUNTRY
Bechgaard; Erik Hellerup DK
Gizurarson; Sveinbjorn Keflavik IS
Hjortkj.ae butted.r; Rolf Kuhlman Humleb.ae butted.r DK

US-CL-CURRENT: 514/2; 514/4, 530/300

#### ABSTRACT:

A method for administering a therapeutically effective amount of a biologically active substance to the circulatory system of a mammal including administering a pharmaceutical composition having a total volume of 1-1000 .mu.l to a nasal mucosal membrane of the mammal, the pharmaceutical composition including the therapeutically effective amount of the biologically active substance dissolved or suspended in a volume of 1-1000 .mu.l of an n-ethylene glycol containing vehicle including at least one n-ethylene glycol represented by the formula:

H(OCH.sub.2 CH.sub.2).sub.p OH

wherein p is from 1 to 8, so that upon administration of the pharmaceutical composition to the nasal mucosal membrane, absorption of the biologically active substance through the mucosal membrane and into the blood stream of the mammal rapidly takes place and thereby allows the biologically active substance to exert its therapeutic effect.

30 Claims, 16 Drawing figures Exemplary Claim Number: 1 Number of Drawing Sheets: 16

Full Title Citation Front	itation Front Review Classification C		Sequences Attachments	KWC Draw Desc Imag					
6. Document ID:	: US 5534496 A								
L1: Entry 6 of 9		File	: USPT	Jul 9, 1996					

US-PAT-NO: 5534496

DOCUMENT-IDENTIFIER: US 5534496 A

TITLE: Methods and compositions to enhance epithelial drug transport

DATE-ISSUED: July 9, 1996

INVENTOR-INFORMATION:

NAME CITY STATE ZIP CODE COUNTRY

Lee; Vincent H. Monterey Park CA Yen; Wan-Ching Columbus OH

US-CL-CURRENT: 514/17; 424/434, 514/18, 514/19, 530/330, 530/331

#### ABSTRACT:

Methods and compositions provided for enhancing the transport of drugs (including peptides, oligonucleotides, proteins and conventional drugs) across epithelial cells at mucosal sites. The methods and compositions include the use of a peptide comprising at least two amino acids, such as Pro-Leu-Gly-Pro-Arg or Pro-Leu, and a protective group such as phenylazo-benzyloxycarbonyl, N-methyl, t-butyloxycarbonyl, fluoroenylmethyloxycarbonyl or carbobenzoxy, at the N-terminus, or in a mixture of such peptides in a sufficient amount to enhance the drug transport across epithelial cells at mucosal sites. Preferably, the peptide comprises 2 to 5 amino acids; the N-terminal amino acids are preferably Pro-Leu. The peptide with the drug are introduced to the mucosal site in a physical mixture, a conjugated form or by a microcapsule, microsphere, liposome, cell, bacteria, virus or food vesicle carrier by an oral, nasal, pulmonary, buccal, rectal, transdermal, vaginal or ocular route.

8 Claims, 37 Drawing figures Exemplary Claim Number: 1 Number of Drawing Sheets: 11

Full Title Citation Front Review Classifica	ition Date Reference Sequences Attachine	ents KWIC Draw Desc Image
7. Document ID: US 5428006	A	
L1: Entry 7 of 9	File: USPT	Jun 27, 1995

US-PAT-NO: 5428006

DOCUMENT-IDENTIFIER: US 5428006 A

TITLE: Method of administering a biologically active substance

DATE-ISSUED: June 27, 1995

INVENTOR - INFORMATION:

NAME CITY STATE ZIP CODE COUNTRY
Bechgaard; Erik Hellerup DK
Gizurarson; Sveinbjorn Keflavik IS
Hjortkjaer; Rolf K. Humlebaer DK

US-CL-CURRENT: 514/3; 514/2, 514/4, 530/303, 530/307, 530/311, 530/313

#### ABSTRACT:

A method for administering a therapeutically effective amount of a biologically active substance to the circulatory system of a mammal including administering a pharmaceutical composition having a total volume of 1-1000 .mu.1 to a nasal mucosal membrane of the mammal, the pharmaceutical composition including the therapeutically effective amount of the biologically active substance dissolved or suspended in a volume of 1-1000 .mu.1 of a n-glycofurol-containing vehicle including at least one n-glycofurol represented by the formula: ##STR1## wherein n is from 1 to 8, so that upon administration of the pharmaceutical composition to the nasal mucosal membrane, absorption of the biologically active substance through the mucosal membrane and into the blood stream of the mammal rapidly takes place and thereby allows the biologically active substance to exert its therapeutic effect.

22 Claims, 12 Drawing figures Exemplary Claim Number: 1 Number of Drawing Sheets: 12

Full	Title	Citation Fron	t Review	Classification	Date	Reference	Sequences	Attachments	KWIC	Draw, Desc	Image
 					***************************************						***************************************
	8.	Document II	D: US 53	97771 A							

File: USPT

US-PAT-NO: 5397771

L1: Entry 8 of 9

DOCUMENT-IDENTIFIER: US 5397771 A

TITLE: Pharmaceutical preparation

DATE-ISSUED: March 14, 1995

INVENTOR-INFORMATION:

NAME CITY STATE ZIP CODE COUNTRY
Bechgaard; Erik Hellerup DK
Gizurarson; Sveinbjorn Keflavik IS
Hjortkjaer; Rolf K. Humlebaer DK

US-CL-CURRENT: 514/2; 514/3, 514/4, 530/303, 530/307, 530/311, 530/313

Mar 14, 1995

Record List Display

'ABSTRACT:

A pharmaceutical preparation for application of an effective amount of one or more biologically active substance(s) to a mucosal membrane of a mammal comprising an n-glycofurol represented by the formula I: ##STR1## wherein n is 1 to 4 in an amount from: 0.1-30% preferably 0.1-20% most preferably 1-15% in water, or in vegetable oil or n-ethylene glycol(s) represented by formula II:

H(OCH.sub.2 CH.sub.2).sub.p OH

wherein p is 2 to 8, or in a mixture thereof. Nasal administration of the preparation produces a high plasma concentration of the pharmaceutically active substance(s) nearly as rapid as by i.v. administration.

29 Claims, 16 Drawing figures Exemplary Claim Number: 1 Number of Drawing Sheets: 16

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments

KWMC | Draw Desc | Image

# 9. Document ID: JP 2002532558 W WO 200037099 A2 AU 200019878 A EP 1140150 A2 CN 1334743 A

L1: Entry 9 of 9

File: DWPI

Oct 2, 2002

DERWENT-ACC-NO: 2000-452127

DERWENT-WEEK: 200279

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TITLE: Stimulating mucociliary clearance rate of mucus and sputum in lung airways for treating lung diseases such as cystic fibrosis and bronchitis involves administering a Kunitz-type serine protease inhibitor

INVENTOR: HALL, R; NEWTON, B B ; POLL, C T ; TAYLOR, W J A

PRIORITY-DATA: 1999US-0441966 (November 17, 1999), 1998US-0218913 (December 22, 1998)

#### PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 2002532558 W	October 2, 2002		227	A61K038/55
WO 200037099 A2	June 29, 2000	E	173	A61K038/57
AU 200019878 A	July 12, 2000		000	A61K038/57
EP 1140150 A2	October 10, 2001	E	000	A61K038/57
CN 1334743 A	February 6, 2002		000	A61K038/57

INT-CL (IPC): A61 K 9/12; A61 K 9/72; A61 K 38/55; A61 K 38/57; A61 K 47/02; A61 P  $\frac{11}{00}$ ; A61 P  $\frac{27}{16}$ ; A61 P  $\frac{27$ 

ABSTRACTED-PUB-NO: WO 200037099A BASIC-ABSTRACT:

NOVELTY - Accelerating the rate of mucociliary clearance in a subject comprising administering a composition (I) comprising a Kunitz-type serine protease inhibitor (KSPI).

ACTIVITY - Antiinflammatory. The effect of the Kunitz family serine protease inhibitor, bikunin, was studied on sheep tracheal mucus velocity (TMV) over 8 hours after treatment with bikunin. 9 mg bikunin (3 ml of 3 mg/ml) was administrated by a nebulized aerosol to the airways and to measure TMV, 5-10 radiopaque Teflon (RTM) particles were insufflated into the trachea via a catheter placed within the endotracheal tube. The movement of the Teflon (RTM) particles was then measured for 1 minute. TMV was calculated from the average distance in a cephalad direction traveled per minute for 5 - 10 Teflon particles. Baseline TMV was measured immediately prior to administration of the aerosol for 8 hours with an interval of 1 hour. The results showed that bikunin aerosol delivered to sheep airways significantly increased TMV at 8 hours compared to the same time for a group of animals receiving phosphate buffered saline (PBS) vehicle aerosol.

\*MECHANISM OF ACTION - Serine protease inhibitor.

USE - Kunitz-type serine protease inhibitors are useful for stimulating the rate of mucociliary clearance of mucus and sputum in the lung airways (claimed). The inhibitors are useful for treating lung diseases such as cystic fibrosis, chronic bronchitis, bronchiectasis and chronic sinusitis and glue ear caused by retention and accumulation of mucus.

ADVANTAGE - The composition reduces or eliminates mucus and sputum in lung airways in patients with chronic obstructive lung disease and reduces the risk of secondary lung infections and other adverse side effects, as well as avoiding or delaying the need for lung transplant surgery in cystic fibrosis patients. Inhibitors are human proteins and therefore reduce the risk of kidney damage on administration of large doses of Trasylol proteins.

Full Title Citation Front Review Classification Date Reference Sequences Attachments	KMIC   Draw, Desc   Image
Generate Collection Print	
Terms	Documents
mucociliary clearance and (kunitz or bikunin or aprotinin)	9

Display Format: - Change Format

Previous Page Next Page

=> file .nash => s mucociliary clearance and kunitz O FILE MEDLINE 1 FILE CAPLUS L2 1 FILE SCISEARCH L3 O FILE LIFESCI L4 1.5 O FILE BIOSIS 1.6 O FILE EMBASE TOTAL FOR ALL FILES 2 MUCOCILIARY CLEARANCE AND KUNITZ

=> dup rem 17

PROCESSING COMPLETED FOR L7

2 DUP REM L7 (0 DUPLICATES REMOVED)

=> d ibib abs

ANSWER 1 OF 2 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 2001:513776 SCISEARCH

THE GENUINE ARTICLE: 447AR

Na+ transport in normal and CF human bronchial epithelial TITLE:

cells is inhibited by BAY 39-9437

AUTHOR: Bridges R J (Reprint); Newton B B; Pilewski J M; Devor D

C; Poll C T; Hall R L

CORPORATE SOURCE: Univ Pittsburgh, Dept Cell Biol & Physiol, 3500 Terrace

> St, S310 Biomed Sci Tower, Pittsburgh, PA 15261 USA (Reprint); Univ Pittsburgh, Dept Cell Biol & Physiol, Pittsburgh, PA 15261 USA; Bayer Pharmaceut Div, Slough SL2

4LY, Berks, England

USA; England COUNTRY OF AUTHOR:

SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-LUNG CELLULAR AND MOLECULAR

PHYSIOLOGY, (JUL 2001) Vol. 281, No. 1, pp. L16-L23. Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE,

BETHESDA, MD 20814 USA.

ISSN: 1040-0605.

Article; Journal DOCUMENT TYPE: LANGUAGE: English

REFERENCE COUNT:

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

To test the hypothesis that Na+ transport in human bronchial epithelial (HBE) cells is regulated by a protease-mediated mechanism, we investigated the effects of BAY 39-9437, a recombinant Kunitz-type serine protease inhibitor, on amiloride-sensitive short-circuit current of normal [non-cystic fibrosis (CF) cells] and CF HBE cells. Mucosal treatment of non-CF and CF HBE cells with BAY 39-9437 decreased the short-circuit current, with a half-life of similar to 45 min. At 90 min, BAY 39-9437 (470 nM) reduced Na+ transport by similar to 70%. The inhibitory effect of BAY 39-9437 was concentration dependent, with a half-maximal inhibitory concentration of similar to 25 nM. Nai transport was restored to control levels, with a half-life of similar to 15 min, on washout of BAY 39-9437. In addition, trypsin (1 muM) rapidly reversed the inhibitory effect of BAY 39-9437. These data indicate that Na+ transport in HBE cells is activated by a BAY 39-9437-inhibitable, endogenously expressed serine protease. BAY 39-9437 inhibition of this serine protease maybe of therapeutic potential for the treatment of Na+ hyperabsorption in CF.

=> d ibib abs 2

ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS ACCESSION NUMBER: 2000:441647 CAPLUS

DOCUMENT NUMBER: 133:84295

TITLE: Kunitz-type serine proteinase inhibitors for

accelerating the rate of mucociliary

INVENTOR(S): Hall, Roderick; Poll, Christopher T.; Newton, Benjamin

B.; Taylor, William J. A.

PATENT ASSIGNEE(S): Bayer Aktiengesellschaft, Germany SOURCE:

PCT Int. Appl., 173 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent English

LANGUAGE:

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

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PATENT NO.
                       KIND DATE
                                              APPLICATION NO. DATE
                      ----
                                              WO 1999-GB4381 19991222
     WO 2000037099
                      A2
                             20000629
     WO 2000037099
                        A3
                             20001026
         W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR,
             CZ, CZ, DE, DE, DK, DK, DM, EE, EE, ES, FI, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS,
             LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
             ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
             DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
             CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     EP 1140150
                        A2 20011010
                                             EP 1999-963636 19991222
         R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
     JP 2002532558
                        T2 20021002
                                              JP 2000-589209
                                                               19991222
PRIORITY APPLN. INFO.:
                                           US 1998-218913 A 19981222
                                                            A 19991117
W 19991222
                                           US 1999-441966
                                           WO 1999-GB4381
```

The instant invention provides for a compn. and method for using Kunitz-type serine protease inhibitors, e.g., aprotinin or bikunin, for stimulating the rate of mucociliary clearance of mucus and sputum in lung airways of subjects afflicted with mucociliary dysfunctions such as cystic fibrosis.

=> s mucociliary clearance and bikunin TOTAL FOR ALL FILES L15 1 MUCOCILIARY CLEARANCE AND BIKUNIN

=> d ibib abs

L15 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS ACCESSION NUMBER: 2000:441647 CAPLUS

DOCUMENT NUMBER:

133:84295

TITLE:

Kunitz-type serine proteinase inhibitors for

accelerating the rate of mucociliary

INVENTOR(S):

Hall, Roderick; Poll, Christopher T.; Newton, Benjamin

B.; Taylor, William J. A.

PATENT ASSIGNEE(S):

Bayer Aktiengesellschaft, Germany

SOURCE:

PCT Int. Appl., 173 pp. CODEN: PIXXD2

Patent

DOCUMENT TYPE:

English

LANGUAGE:

FAMILY ACC. NUM. COUNT: 1 PATENT INFORMATION:

PATENT NO.			KI	ND	DATE			А	PPLI	CATI	ON N	٥.	DATE				
WO	WO 2000037099 A2			2	2000	0629		W	0 19	99-G	B438.	1	19991222				
WO	WO 2000037099			А	3	2000	1026										
	W:	ΑE,	AL,	AM,	AT,	ΑT,	AU,	AZ,	BA,	BB,	BG,	BR,	BY,	CA,	CH,	CN,	CR,
		CZ,	CZ,	DE,	DE,	DK,	DK,	DM,	EE,	EE,	ES,	FI,	FI,	GB,	GD,	GE,	GH,
		GM,	HR,	ΗU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	KR,	KZ,	LC,	LK,	LR,	LS,
		LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	NO,	ΝZ,	PL,	PT,	RO,	RU,
	•	SE,	SG,	SI,	SK,	sĸ,	SL,	ТJ,	TM,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VN,
		ZA,	ZW,	AM,	ΑZ,	BY,	KG,	ΚZ,	MD,	RU,	TJ,	TM					
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		DK,	ES,	FI,	FR,	GB,	GR,	ΙE,	ΙT,	LU,	MC,	NL,	PT,	SE,	BF,	ВJ,	CF,
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ΕP	1140	150		A	A2 20011010				EP 1999-963636 19991222								
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR.	GB,	GR,	IT,	LI.	LU,	NL.	SE,	MC.	PT.

IE, SI, LT, LV, FI, RO

JP 2002532558 T2 20021002

PRIORITY APPLN. INFO.:

JP 2000-589209 19991222 US 1998-218913 A 19981222 US 1999-441966 A 19991117 WO 1999-GB4381 W 19991222

AB The instant invention provides for a compn. and method for using Kunitz-type serine protease inhibitors, e.g., aprotinin or **bikunin**, for stimulating the rate of **mucociliary clearance** of mucus and sputum in lung airways of subjects afflicted with mucociliary dysfunctions such as cystic fibrosis.

=> s bikunin TOTAL FOR ALL FILES L22 872 BIKUNIN

=> 122 and (poteinase inhibitor or protease inhibitor)

L22 IS NOT A RECOGNIZED COMMAND

The previous command name entered was not recognized by the system. For a list of commands available to you in the current file, enter "HELP COMMANDS" at an arrow prompt (=>).

=> s 122 and (poteinase inhibitor or protease inhibitor)

TOTAL FOR ALL FILES

L29 213 L22 AND (POTEINASE INHIBITOR OR PROTEASE INHIBITOR)

=> s 122 and sodium
TOTAL FOR ALL FILES

L36 56 L22 AND SODIUM

=> s 136 and 129
TOTAL FOR ALL FILES
L43 8 L36 AND L29

=> s 143 not 2000-2002/py TOTAL FOR ALL FILES

L50 3 L43 NOT 2000-2002/PY

=> dup rem 150

PROCESSING COMPLETED FOR L50

L51 2 DUP REM L50 (1 DUPLICATE REMOVED)

=> d ibib abs

L51 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1997:290844 BIOSIS DOCUMENT NUMBER: PREV199799590047

TITLE: Human pre-alpha-inhibitor: Isolation from a by-product of

industrial scale plasma fractionation and structural

analysis of its H3 heavy chain.

AUTHOR(S): Mizon, Charlotte; Heron, Antoine; Capon, Callioppe;

Sautiere, Pierre; Michalski, Catherine; Sesboue, Richard;

Mizon, Jacques (1)

CORPORATE SOURCE: (1) Lab. Biochimie, Fac. Pharmacie, Ave. du Professeur

Laguesse, B.P. 83, F-59006 Lille France

SOURCE: Journal of Chromatography B, (1997) Vol. 692, No. 2, pp.

281-291.

ISSN: 0378-4347.

DOCUMENT TYPE: Article LANGUAGE: English

AB Pre-alpha-inhibitor (P-alpha-I) is a serine proteinase inhibitor from human plasma. It comprises **bikunin** (BK) responsible for antiprotease activity, covalently linked to a heavy chain H3. Here we describe its isolation from a side fraction of an industrial preparation of plasma clotting factors. By using a highly specific polyclonal antiserum prepared from rabbit immunized with a H3P polypeptide obtained in a bacterial expression system, we were able to identify the fractions containing P-alpha-I. Then, taking advantage of the differential affinity of the members of the inter-alpha-inhibitor family (I-alpha-I) for heparin-Sepharose and blue-Sepharose, we isolated P-alpha-I. Its specific antitryptic activity was 580 IU/g, higher than that of I-alpha-I: 420

IU/g. Its M-r, determined by **sodium** dodecyl sulfate polyacrylamide gel electrophoresis, with or without prior reduction, was 130 000. Its peptide chains were identified by N-terminal sequencing. The H3 heavy chain was isolated from P-alpha-I by alkaline dissociation and anion-exchange chromatography. Its electrophoretic mobility was compared to that of the H1 and H2 heavy chains of I-alpha-I. In reducing conditions, it was quite similar to that of H2 (M-r 85 000) but clearly different from that of H1 (M-r 78 000). Thus, the so-determined apparent M-r of H3 was overestimated since its molecular mass determined by MALDI-TOF was 74 100. This result agrees with the proposed structure for H3. Indeed, by carbohydrate analysis and PNGase F digestion, we demonstrate that the two potential N-glycosylation sites present in the core-protein (theoretical mass: 69 454) are really occupied by two N-glycans, probably of biantennary type.

#### => d ibib abs 2

L51 ANSWER 2 OF 2 MEDLINE DUPLICATE 1

ACCESSION NUMBER: 97018241 MEDLINE

DOCUMENT NUMBER: 97018241 PubMed ID: 8864857

TITLE: Inter-alpha-trypsin inhibitor and its related proteins in

Syrian hamster urine and plasma.

AUTHOR: Yamamoto T; Yamamoto K; Sinohara H
CORPORATE SOURCE: Department of Biochemistry, Kinki University School of

Medicine, Osaka.

SOURCE: JOURNAL OF BIOCHEMISTRY, (1996 Jul) 120 (1) 145-52.

Journal code: 0376600. ISSN: 0021-924X.

PUB. COUNTRY: Japan

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199701

ENTRY DATE: Entered STN: 19970128

Last Updated on STN: 19970128 Entered Medline: 19970114

Urinary excretion of trypsin inhibitor increased after injection of a carcinogen, N-nitrosobis(2-oxopropyl)amine, into Syrian hamsters. Two inhibitors were purified to apparent homogeneity from urine collected during the course of the carcinogenesis experiment. Their complete amino acid sequences were determined by Edman degradation of the intact proteins and partially degraded fragments. One corresponded to a hamster liver cDNA clone that hybridized with human bikunin probe [Ide et al, (1994) Biochim, Biophys. Acta 1209, 286-292], except that the protein sequence lacked C-terminal serine and the other was trypstatin, the C-terminal half of the bikunin molecule. Three proteins containing covalently linked bikunin were also identified in pooled blood plasma. They were all dissociated into heavy and light chains by treatment with chondroitinase ABC or 50 mM NaOH, but not by heating at 100 degrees C in the presence of sodium dodecyl sulfate and dithiothreitol, N-terminal amino acid sequence analyses of the native chains and partially degraded fragments thereof revealed that these proteins are (i) human-type inter-alpha-trypsin inhibitor, consisting of heavy chains 1 and 2 and bikunin, (ii) bovine-type inter-alpha-trypsin inhibitor, consisting of heavy chains 2 and 3 and bikunin, and (iii) pre-alpha-trypsin inhibitor, consisting of heavy chain 3 and bikunin. Heterodimer of bikunin /heavy chain 1 or bikunin/heavy chain 2 was not detected. These results suggest that the composition, and hence function, of the inter-alpha-trypsin inhibitor family differs considerably from species to species.

=> s 136 not 2000-2002/py TOTAL FOR ALL FILES L58 37 L36 NOT 2000-2002/PY

=> dup rem 157

PROCESSING COMPLETED FOR L57

L59 9 DUP REM L57 (O DUPLICATES REMOVED)

L59 ANSWER 1 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

1999399055 EMBASE ACCESSION NUMBER:

TITLE: Proteoglycan core protein in human urine and its possible

role on calcium oxalate urolithiasis.

AUTHOR: Yoshimura K.; Miyake O.; Tsujihata M.; Yoshioka T.;

Yamaquchi S.; Koide T.; Takahara S.; Okuyama A.

CORPORATE SOURCE: Dr. K. Yoshimura, Department of Urology, Osaka University

Medical School, 2-2 Yamada-oka, Suita, Osaka 565-0871,

Japan. ky135@uro.med.osaka-u.ac.jp

SOURCE: International Journal of Urology, (1999) 6/11 (567-571).

Refs: 26

ISSN: 0919-8172 CODEN: IJURF3

COUNTRY: Australia

DOCUMENT TYPE: Journal; Article

General Pathology and Pathological Anatomy FILE SEGMENT: 005

028 Urology and Nephrology 029 Clinical Biochemistry

LANGUAGE: English SUMMARY LANGUAGE: English

Background: There are only a few papers reporting on the role of proteoglycan core protein in calcium oxalate stone formation. The present study was carried out to investigate the role of core protein of proteoglycan in human urine on calcium oxalate (CaOx) crystallization. Methods: Proteoglycans were collected from whole human urine. The covalently bound glycosaminoglycans (GAG) of proteoglycans were then digested by GAG lyase. The inhibitory activity on CaOx crystal growth in vitro was measured before and after enzyme digestion of proteoglycans. Sodium dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE) of the core protein of proteoglycans and the analysis of amino acid sequence were performed. Results: The core protein showed significant inhibitory activity on CaOx crystal growth, which scarcely changed when compared with that of proteoglycans before enzyme digestion. The SDS-PAGE revealed that the core protein was a single unit with a molecular weight of 26 kDa and amino acid sequencing demonstrated high homology to interalpha-trypsin inhibitor (ITI) light chain (bikunin) with Kunitz inhibitor domain as a core protein. Conclusions: The results suggested that human urine contains proteoglycans and a major part of them is ITI light chain (bikunin). The Kunitz inhibitor domain, a core protein of bikunin, has significant inhibitory activity on

L59 ANSWER 2 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1999370183 EMBASE

TITLE: Role of urinary bikunin in the inhibition of

calcium oxalate crystallization.

AUTHOR: Atmani F.; Khan S.R.

Dr. S.R. Khan, University of Florida, College of Medicine, CORPORATE SOURCE:

CaOx crystallization without GAG bound covalently to the core protein.

Department of Pathology, Gainesville, FL 32610, United

States. khan@ufl.edu

Journal of the American Society of Nephrology, (1999) SOURCE:

10/SUPPL. 14 (S385-S388).

Refs: 20

ISSN: 1046-6673 CODEN: JASNEU

COUNTRY: United States

DOCUMENT TYPE: Journal; Conference Article FILE SEGMENT: 028 Urology and Nephrology

LANGUAGE: English SUMMARY LANGUAGE: English

Several urinary macromolecules are known to modulate calcium oxalate

(CaOx) crystallization. One of these is urinary bikunin, the

light chain of inter-.alpha.-inhibitor. Bikunin has been

demonstrated to be an efficient inhibitor of CaOx crystal growth; however, its inhibitory activity against other events in CaOx crystallization has

not been fully investigated. To assess the potential of urinary bikunin as an effective inhibitor, its effects on CaOx crystal

nucleation and aggregation were evaluated. Nucleation and aggregation of CaOx crystals were studied by measuring turbidity at 620 nm. In the nucleation assay, crystallization was induced by mixing calcium chloride

and sodium oxalate, at final concentrations of 3 and 0.5 mM,

respectively. Both solutions were buffered with 0.05 M Tris, 0.15 M NaCl, pH 6.5. Nucleation measurements were performed at 37.degree.C, with stirring at 800 rpm. Inhibition of nucleation was estimated by comparing the induction time in the presence of the inhibitor with control values. In the aggregation assay, the optical density of the solution containing CaOx monohydrate crystals was monitored. Inhibition of aggregation was evaluated by comparing the turbidity slope in the presence of the inhibitor with control values. The data showed that urinary bikunin, at concentrations of 2.5 to 20 .mu.g/ml, retarded crystal nucleation by 67 to 58% and inhibited crystal aggregation by 59 to 80%. According to these results, it seems that urinary bikunin is an efficient inhibitor of crystal nucleation and aggregation. Its presence in the kidneys and urine may protect subjects against CaOx crystallization and kidney stone formation.

L59 ANSWER 3 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

1999091047 EMBASE ACCESSION NUMBER:

TITLE: Differential expression of urinary inter-.alpha.-trypsin

inhibitor trimers and dimers in normal compared to active

calcium oxalate stone forming men.

Marengo S.R.; Resnick M.I.; Yang L.; Chung J.-Y. AUTHOR:

CORPORATE SOURCE: S.R. Marengo, Urology Research Laboratories, School of

Medicine, 2109 Adelbert Rd., Cleveland, OH 44106, United

States

SOURCE: Journal of Urology, (1998) 159/5 (1444-1450).

Refs: 24

ISSN: 0022-5347 CODEN: JOURAA

COUNTRY: United States DOCUMENT TYPE: Journal; Article

Urology and Nephrology FILE SEGMENT: 028

LANGUAGE: English SUMMARY LANGUAGE:

English Purpose: We determine if the immunoreactive profile of urinary inter-.alpha.-trypsin inhibitor can be used to distinguish between normal individuals and individuals with calcium oxalate stone disease. Materials and Methods: Urinary proteins were dialyzed against water (15 kDa. molecular weight cutoff), lyophilized and resolved by  ${\tt sodium}$ dodecyl sulfate-polyacrylamide gel electrophoresis (6% acrylamide, reducing conditions) followed by Western blot. Inter-.alpha.-trypsin immunoreactive proteins were detected by enhanced chemiluminescence. Stone formation was confirmed to be active radiologically or passed as stone or gravel within 12 months of the sample. Stone composition was confirmed crystallographically. Normal individuals had no personal or familial history of urolithiasis and matched stone forming patients regarding race (white) and age (23 to 71 years old). Urine from a total of 101 individuals was analyzed. Results: The intact inter-.alpha.-trypsin trimer (.apprx.220 to 240 kDa.) and heavy chain (HC) 2-bikunin/HC1bikunin dimers (.apprx.115 to 130 kDa.) were detected more often in stone forming men (23 of 26 [89%] and 26 of 26 [100%], respectively) than in normal individuals (6 of 26 [23%] and 5 of 26 [19%], respectively, p < 0.0001). In those normal individuals who expressed inter-.alpha.-trypsin trimer and HC-bikunins the relative intensities were 5.3 .+-. 1.4% and 16.3 .+-. 17.1% of the stone forming controls, respectively. The identity of high molecular weight-inter-.alpha.- trypsin immunoreactive bands was confirmed using antibodies against the individual subunits (HC1, HC2, HC3, bikunin ). In contrast to men high molecular weight-inter-.alpha.-trypsin's were readily detected in normal and stone forming women with equal frequency (inter-.alpha.-trypsin-trimer p = 0.1337, HC- bikunins p = 0.2836): inter-.alpha.-trypsin-trimer 17 of 18 [94%] and 9 of 13 [77%]; HC-bikunins 17 of 18 [94%] and 10 of 13 [85%]). Inter-.alpha.-trypsin- trimer and HC-bikunins, respectively, were detected in 2 and 5 of 10 patients with chronic renal disease. Expression was not related to hematuria or proteinuria. Conclusions: Immunoreactive profiles of urinary proteins may be able to be developed into a useful diagnostic tool to identify active stone formation, although a separate panel may be required for men and women. It is possible that these differences may provide clues as to why the incidence of stone disease is higher in men than women.

1998343313 EMBASE ACCESSION NUMBER:

Bikunin present in human peritoneal fluid is in TITLE:

part derived from the interaction of serum with peritoneal

1

THE PERSON NAMED IN

mesothelial cells.

AUTHOR: Thomas G.J.; Yung S.; Davies M.

Dr. M. Davies, Institute of Nephrology, Royal Infirmary, CORPORATE SOURCE:

Cardiff CF2 1SZ, Wales, United Kingdom. daviesm6@cf.ac.uk American Journal of Pathology, (1998) 153/4 (1267-1276).

Refs: 57

ISSN: 0002-9440 CODEN: AJPAA4

COUNTRY: United States DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 0.05 General Pathology and Pathological Anatomy

LANGUAGE: English SUMMARY LANGUAGE: English

SOURCE:

We recently reported that peritoneal fluid mainly contains two proteoglycans; one is the interstitial proteoglycan referred to as decorin, and the other an uncharacterized small chondroitin sulfate proteoglycan. In the present study, we have used a two-step process to isolate the small chondroitin sulfate proteoglycan free of decorin. The purified molecule ran as a single band on **sodium** dodecyl sulfate-polyacrylamide gel electrophoresis with apparent molecular mass 50 kd made up of a chondroitin-4-sulfate glycosaminoglycan chain and a 30-kd core protein. NH2-terminal analysis of the core protein showed significant sequence homology with bikunin, a component of the human inter-.alpha.-trypsin inhibitor (I.alpha.I) family. A Western blot analysis using anti-human inter-.alpha.-trypsin inhibitor confirmed the identity of the small chondroitin sulfate proteoglycan as bikunin , and a trypsin inhibitor counterstain assay confirmed its anti-trypsin activity. Examination of serum from patients receiving continuous peritoneal dialysis suggests that free bikunin in peritoneal fluid may be the result of leakage of serum proteins into the peritoneum. Our findings further show that the interaction of serum with peritoneal mesothelial cells offers a new and novel explanation for the presence of bikunin in peritoneal fluid.

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ACCESSION NUMBER: 1998229876 EMBASE

TITLE: Inter-.alpha.-inhibitor in urine and calcium oxalate

urinary crystals.

AUTHOR: Dawson C.J.; Grover P.K.; Ryall R.L.

CORPORATE SOURCE: Prof. R.L. Ryall, Department of Surgery, Flinders Medical

Centre, Bedford Park, SA 5042, Australia

SOURCE: British Journal of Urology, (1998) 81/1 (20-26).

Refs: 28

ISSN: 0007-1331 CODEN: BJURAN

United Kingdom COUNTRY:

DOCUMENT TYPE: Journal: Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy

028 Urology and Nephrology 029 Clinical Biochemistry

LANGUAGE: English SUMMARY LANGUAGE: English

Objective. To determine which chains of inter-.alpha.-inhibitor (I.alpha.I) are present in urine and whether they are also round in calcium oxalate (CaOx) crystals generated in human urine. Materials and methods. Fresh urine specimens were collected from five women and five men with no previous history of stone disease. An aliquot of each urine was retained for analysis, the remainder treated with a standard load of oxalate and the CaOx crystals precipitated from each specimen demineralized with ethylenediamine tetracetic acid. The resulting organic extracts from crystals and their corresponding urine samples were subjected to sodium dodecyl sulphate gel electrophoresis analysis and Western blotting using a commercial polyclonal antibody to I.alpha.I. Results. Heavy chain 1 (H1) and 2 (H2) of I.alpha.I were commonly found in every urine sample, and in the CaOx crystals precipitated from those urine samples. Several protein bands were visible in urine samples from both sexes in the molecular mass range 25-70 kDa, which may be bikunin or its fragments. As well as H1 and H2, the crystals from both sexes contained a protein band at .simeq. 33 kDa. In many cases there appeared to be no direct relationship between the

proteins detected in the crystals and the urine samples from which they were derived, which probably reflects the well known instability of I.alpha.I and the occurrence of a range of bikunin fragments in urine. Conclusion. These results show for the first time that H1 and H2, are present in human urine and urinary CaOx crystals, that the bikunin chain of I.alpha. I is not the only part of the molecule capable of participating in CaOx crystallization in urine, and in theory at least, in the regulation of crystallization events in stone formation. It is also apparent that significant fragmentation of I.alpha.I occurs both in vivo and in vitro, and this must be considered in any study attempting to elucidate the influence of this protein in the formation of CaOx stones.

L59 ANSWER 6 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

97155611 EMBASE ACCESSION NUMBER:

DOCUMENT NUMBER: 1997155611

TITLE: Human pre-.alpha.-inhibitor: Isolation from a by-product of

industrial scale plasma fractionation and structural

analysis of its H3 heavy chain.

AUTHOR: Mizon C.; Heron A.; Capon C.; Sautiere P.; Michalski C.;

Sesboue R.; Mizon J.

CORPORATE SOURCE: J. Mizon, Lab. Biochimie (DRED EA 1052), Faculte de

Pharmacie, Avenue du Professeur Laguesse, F-59006 Lille,

France

SOURCE: Journal of Chromatography B: Biomedical Applications,

(1997) 692/2 (281-291).

Refs: 23

ISSN: 0378-4347 CODEN: JCBBEP

S 0378-4347(97)00012-1 PUBLISHER IDENT.:

Netherlands

DOCUMENT TYPE: Journal: Article FILE SEGMENT: 025 Hematology

029 Clinical Biochemistry

LANGUAGE: English SUMMARY LANGUAGE: English

Pre-.alpha.-inhibitor (P.alpha.I) is a serine proteinase inhibitor from human plasma. It comprises bikunin (BK) responsible for antiprotease activity, covalently linked to a heavy chain H3. Here we describe its isolation from a side fraction of an industrial preparation of plasma clotting factors. By using a highly specific polyclonal antiserum prepared from rabbit immunized with a H3P polypeptide obtained in a bacterial expression system, we were able to identify the fractions containing P.alpha.I. Then, taking advantage of the differential affinity of the members of the inter-a-inhibitor family (I.alpha.I) for heparin-Sepharose and blue-Sepharose, we isolated P.alpha.I. Its specific antitryptic activity was 580 IU/g, higher than that of I.alpha.I: 420 IU/g. Its M(r), determined by **sodium** dodecyl sulfate polyacrylamide gel electrophoresis, with or without prior reduction, was 130 000. Its peptide chains were identified by N-terminal sequencing. The H3 heavy chain was isolated from P.alpha. I by alkaline dissociation and anion-exchange chromatography. Its electrophoretic mobility was compared to that of the H1 and H2 heavy chains of I.alpha.I. In reducing conditions, it was quite similar to that of H2 (M(r) 85 000) but clearly different from that of H1 (M(r) 78 000). Thus, the so-determined apparent M(r) of H3 was overestimated since its molecular mass determined by MALDI-TOF was 74 100. This result agrees with the proposed structure for H3. Indeed, by carbohydrate analysis and PNGase F digestion, we demonstrate that the two potential N-glycosylation sites present in the core-protein (theoretical mass: 69 454) are really occupied by two N-glycans, probably of biantennary type.

L59 ANSWER 7 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 96239053 EMBASE

DOCUMENT NUMBER: 1996239053

TITLE: Inter-.alpha.-trypsin inhibitor and its related proteins in

Syrian hamster urine and plasma.

AUTHOR: Yamamoto T.; Yamamoto K.; Sinohara H.

CORPORATE SOURCE: Department of Biochemistry, Kinki University School of

Medicine, Osaka-Sayama, Osaka 589, Japan

SOURCE: Journal of Biochemistry, (1996) 120/1 (145-152).

ISSN: 0021-924X CODEN: JOBIAO

COUNTRY: Japan

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English SUMMARY LANGUAGE: English

Urinary excretion of trypsin inhibitor increased after injection of a carcinogen, N-nitrosobis(2-oxopropyl)amine, into Syrian hamsters. Two inhibitors were purified to apparent homogeneity from urine collected during the course of the carcinogenesis experiment. Their complete amino acid sequences were determined by Edman degradation of the intact proteins and partially degraded fragments. One corresponded to a hamster liver cDNA clone that hybridized with human bikunin probe, except that the protein sequence lacked C-terminal serine and the other was trypstatin, the C-terminal half of the bikunin molecule. Three proteins containing covalently linked bikunin were also identified in pooled blood plasma. They were all dissociated into heavy and light chains by treatment with chondroitinase ABC or 50 mM NaOH, but not by heating at 100.degree.C in the presence of sodium dodecyl sulfate and dithiothreitol. N-terminal amino acid sequence analyses of the native chains and partially degraded fragments thereof revealed that these proteins are (i) human-type inter-.alpha.-trypsin inhibitor, consisting of heavy chains 1 and 2 and bikunin, (ii) bovine-type inter-.alpha.-trypsin inhibitor, consisting of heavy chains 2 and 3 and bikunin, and (iii) pre-.alpha.-trypsin inhibitor, consisting of heavy chain 3 and bikunin. Heterodimer of bikunin /heavy chain 1 or bikunin/heavy chain 2 was not detected. These results suggest that the composition, and hence function, of the inter-.alpha.-trypsin inhibitor family differs considerably from species to species.

L59 ANSWER 8 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

93118658 EMBASE ACCESSION NUMBER:

DOCUMENT NUMBER: 1993118658

TITLE: Presence of the protein-glycosaminoglycan-protein covalent

cross-link in the inter-.alpha.-inhibitor-related

proteinase inhibitor heavy chain 2/**bikunin**.
Enghild J.J.; Salvesen G.; Thogersen I.B.; Valnickova Z.; AUTHOR:

Pizzo S.V.; Hefta S.A.

CORPORATE SOURCE: Dept. of Pathology, Duke University Medical Ctr., P.O. Box

3712, Durham, NC 27710, United States

Journal of Biological Chemistry, (1993) 268/12 (8711-8716). SOURCE:

ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English SUMMARY LANGUAGE: English

HC2/bikunin is a human plasma proteinase inhibitor composed of two polypeptide chains that resist dissociation under reducing conditions in SDS- polyacrylamide gel electrophoresis. This observation suggests that a nondisulfide cross-link is responsible for the association of these two polypeptide chains. In this study, we have utilized a variety of techniques to investigate the structural basis for this observation. We show that the cross-link between the two protein chains is sensitive to chondroitin sulfate-degrading enzymes and to 50 mM NaOH, properties shared by the protein-glycosaminoglycan-protein cross-link found in the related pre-.alpha.- inhibitor (Enghild, J. J., Salvesen, G., Hefta, S., Thogersen, I. B., Rutherfurd, S., and Pizzo, S. V. (1991) J. Biol. Chem. 266, 747-751). Biochemical and mass spectrometric analysis of the peptides containing the cross-link indicate that it is mediated by a chondroitin-4-sulfate chain that originates from a typical O-glycosidic link to Ser10 of **bikunin**. The COOH- terminal Asp648 residue of heavy chain 2 is esterified via the .alpha.-carbon to C-6 of an internal N-acetylgalactosamine of the chondroitin-4-sulfate chain. This suggests that the protein-glycosaminoglycan-protein cross-link that assembles the chains of pre-.alpha.-inhibitor is identical to that which assembles HC2/ bikunin, and is probably a characteristic of the bikunin proteins.

L59 ANSWER 9 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V. ACCESSION NUMBER: 92209773 EMBASE

DOCUMENT NUMBER: 1992209773

TITLE: Biosynthesis of bikunin (urinary trypsin

inhibitor) in rat hepatocytes.

AUTHOR: Sjoberg E.M.; Fries E.

CORPORATE SOURCE: Med./Physiological Chemistry Dept., Biomedical Center,

University of Uppsala, S-751 23 Uppsala, Sweden

SOURCE: Archives of Biochemistry and Biophysics, (1992) 295/2

(217-222).

ISSN: 0003-9861 CODEN: ABBIA4

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology

029 Clinical Biochemistry

048 Gastroenterology

LANGUAGE: English
SUMMARY LANGUAGE: English

AB One of the major sulfated proteins secreted by rat hepatocytes contains a low-sulfated chondroitin sulfate chain and its apparent molecular mass upon **sodium** dodecyl sulfate/polyacrylamide gel electrophoresis shifts from 40 to 28 kDa upon chondroitinase ABC treatment (E. M. Sjoberg and E. Fries, 1990, Biochem. J. 272, 113-118). These properties suggest that this protein is the rat homologue of the major trypsin inhibitor of human urine which was recently named **bikunin**. In serum,

human urine which was recently named bikunin. In serum, bikunin occurs mainly as a subunit of the pre-.alpha.-inhibitor and the inter-.alpha.-inhibitor; in these proteins it is covalently linked to the other polypeptides through its chondroitin sulfate chain. Bikunin has been shown to be synthesized by liver cells as a 42-kDa precursor, in which it is linked to .alpha.l-microglobulin by two basic amino acids. We have isolated bikunin from rat urine and prepared antibodies against it. In rat hepatocytes pulse-labeled with [35S]methionine, these antibodies precipitated a labeled protein of 42 kDa. Upon chase, three different labeled proteins were recognized by the antibodies in the medium: one protein of 40 kDa (free bikunin), one of 125 kDa (presumably pre-.alpha.- inhibitor), and one >240 kDa (possibly a protein related to the inter-.alpha.- inhibitor). Pulse-chase experiments with [35S]sulfate showed that these proteins occurred intracellularly as precursors containing .alpha.l- microglobulin. These results demonstrate that the completion of the chondroitin sulfate chain

and its coupling to other polypeptide chains occur before the cleavage of

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L66 353 APROTININ AND CLEARANCE

=> s aprotinin and mucociliary clearance TOTAL FOR ALL FILES

L73 8 APROTININ AND MUCOCILIARY CLEARANCE

the .alpha.1-microglobulin/bikunin precursor.

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L81 ANSWER 1 OF 2 MEDLINE

ACCESSION NUMBER: 92108915 MEDLINE

DOCUMENT NUMBER: 92108915 PubMed ID: 1722377

TITLE: Tissue kallikrein stimulates mucociliary activity in the

rabbit maxillary sinus.

AUTHOR: Lindberg S; Olsson H

CORPORATE SOURCE: Department of Oto-Rhino-Laryngology, University Hospital,

Lund, Sweden.

SOURCE: ACTA OTO-LARYNGOLOGICA, (1991) 111 (6) 1126-32.

Journal code: 0370354. ISSN: 0001-6489.

PUB. COUNTRY:

Sweden

DOCUMENT TYPE:

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE:

English

FILE SEGMENT:

Priority Journals

ENTRY MONTH:

199202

ENTRY DATE:

Entered STN: 19920302

Last Updated on STN: 20000303

Entered Medline: 19920213

AB The in vivo effect of tissue kallikrein on the mucociliary activity in the rabbit maxillary sinus was investigated administering the substance (0.1-5 mU/kg) via a. maxillaris and recording the response with a non-invasive photoelectric technique. Tissue kallikrein accelerated mucociliary activity, with a maximum response for the dose 5 mU/kg (33.7 +/- 13.4% from basal levels, n = 5). The effect had a latency of abut 1 min, with a peak within 2-3 min after the beginning of the administration. The response to tissue kallikrein displayed tachyphylaxis with a second dose producing a weaker response. Pretreatment with the protease inhibitor aprotinin (10,000 KIU bolus/kg) inhibited the action of tissue kallikrein. Tissue kallikrein probably stimulates mucociliary activity by producing lysylbradykinin from kininogen. Bradykinin has in an earlier study been shown to stimulate mucociliary activity.

=> d ibib abs 2

F 2 EMBASE CORYRIGHT 2002 ELSEVTER SCI. B.V

TITLE:

SOURCE:

Mucosal penetration enhancers for facilitation of peptide

and protein drug absorption.

AUTHOR:

Lee V.H.L.; Yamamoto A.; Kompella U.B.

CORPORATE SOURCE:

University of Southern California, School of Pharmacy, Department of Pharmaceutical Sciences, 1985 Zonal Avenue,

Los Angeles, CA 90033, United States

Critical Reviews in Therapeutic Drug Carrier Systems,

1992037735

(1991) 8/2 (91-192). ISSN: 0743-4863 CODEN: CRTSEO

COUNTRY: United States

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 027 Biophysics, Bioengineering and Medical

Instrumentation

052 Toxicology 030 Pharmacology

037 Drug Literature Index

LANGUAGE: English

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RN
     Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro- (9CI) (CA
     INDEX NAME)
OTHER CA INDEX NAMES:
    Pyrazinecarboxamide, N-amidino-3,5-diamino-6-chloro- (7CI, 8CI)
     (3,5-Diamino-6-chloropyrazinoyl)guanidine
CN
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     Amiloride
CN
    Amipramidin
CN
     Guanamprazine
CN
     MK 870
     N-Amidino-3,5-diamino-6-chloropyrazinecarboxamide
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     137053-85-1
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1911 REFERENCES IN FILE CA (1962 TO DATE)
109 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1911 REFERENCES IN FILE CAPLUS (1962 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)
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INVENTOR(S): Berman, Charles L. PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 11 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

CORPORATE SOURCE:

PATENT NO. KIND DATE APPLICATION NO. DATE

US 2002013345 A1 20020131 US 1998-169660 19981009
US 6384081 B2 20020507

AB The instant invention provides a method of inhibiting the formation of metalloproteinase and its species, within the eyes of a patient inflicted with at least one form of retinitis characterized by the presence of metalloproteinase, through the administration of an effective dosage that includes an a tetracycline analog, its salts, conjugates or derivs. In an alternate preferred embodiment of the invention the dosage includes at least one other therapeutic substance in effective combination with a tetracycline analog.

L3 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:508083 CAPLUS

DOCUMENT NUMBER: 135:238438

TITLE: Species Specificity of Amidine-Based Urokinase

Inhibitors

AUTHOR(S): Klinghofer, Vered; Stewart, Kent; McGonigal, Tom;

Smith, Richard; Sarthy, Aparna; Nienaber, Vicki; Butler, Chris; Dorwin, Sarah; Richardson, Paul; Weitzberg, Moshe; Wendt, Mike; Rockway, Todd; Zhao, Xumiao; Hulkower, Keren I.; Giranda, Vincent L.

Departments of Cancer Research and Advanced

Technology, Abbott Laboratories, Abbott Park, IL,

60064-6117, USA

SOURCE: Biochemistry (2001), 40(31), 9125-9131

CODEN: BICHAW; ISSN: 0006-2960

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal LANGUAGE: English

Inhibition of the proteolytic activity of urokinase has been shown to inhibit the progression of tumors in rodent models and is being investigated for use in human disease. Understanding the rodent/human species-specificity of urokinase inhibitors is therefore crit. for interpretation of rodent cancer progression models that use these inhibitors. We report here studies with a panel of 11 diverse urokinase inhibitors in both human and mouse enzymic assays. Inhibitors such as amiloride, B428, and naphthamidine, that occupy only the S1 subsite pocket were found to be nearly equipotent between the human and the murine enzymes. Inhibitors that access addnl., more distal, pockets were significantly more potent against the human enzyme but there was no corresponding potency increase against the murine enzyme. X-ray crystallog. structures of these compds. bound to the serine protease domain of human urokinase were solved and examd. in order to explain the human/mouse potency differences. The differences in inhibitor potency could be attributed to four amino acid residues that differ between murine and human urokinases: 60, 99, 146, and 192. These residues are Asp, His, Ser, and Gln in human and Gln, Tyr, Glu, and Lys in mouse, resp. Compds. bearing a cationic group that interacts with residue 60 will preferentially bind to the human enzyme because of favorable electrostatic interactions. The hydrogen bonding to residue 192 and steric considerations with residues 99 and 146 also contribute to the species specificity. The nonparallel human/mouse enzyme inhibition observations were extended to a cell-culture assay of urokinase-activated plasminogen-mediated fibronectin degrdn. with analogous results. These studies will aid the interpretation of in vivo evaluation of urokinase inhibitors.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2002 ACS ACCESSION NUMBER: 2001:506288 CAPLUS

DOCUMENT NUMBER: 135:298725

TITLE: Na+ transport in normal and CF human bronchial

epithelial cells is inhibited by BAY 39-9437 AUTHOR(S): Bridges, Robert J.; Newton, Ben B.; Pilewski, Joseph

M.; Devor, Daniel C.; Poll, Christopher T.; Hall, Rod

CORPORATE SOURCE: Department of Cell Biology and Physiology, University

of Pittsburgh, Pittsburgh, PA, 15261, USA

SOURCE: American Journal of Physiology (2001), 281(1, Pt. 1), L16-L23

CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal LANGUAGE: English

To test the hypothesis that Na+ transport in human bronchial epithelial (HBE) cells is regulated by a protease-mediated mechanism, we investigated the effects of BAY 39-9437, a recombinant Kunitz-type serine

protease inhibitor, on amiloride-sensitive short-circuit current of normal [non-cystic fibrosis (CF) cells] and CF HBE cells. Mucosal treatment of non-CF and CF HBE cells with BAY 39-9437 decreased the short-circuit current, with a half-life of .apprx.45 min. At 90 min, BAY 39-9437 (470 nM) reduced Na+ transport by .apprx.70%. The inhibitor effect of BAY 39-9437 was concn. dependent, with a half-maximal inhibitory concn. of .apprx.25 nM. Na+ transport was restored to control levels, with a half-life of .apprx.15 min, on washout of BAY 39-9437. In addn., trypsin (1 .mu.M) rapidly reversed the inhibitory effect of BAY 39-9437. These data indicate that Na+ transport in HBE cells is activated by a BAY 39-9437-inhibitable, endogenously expressed serine

protease. BAY 39-9437 inhibition of this serine

protease maybe of therapeutic potential for the treatment of Na+ hyperabsorption in CF.

REFERENCE COUNT:

THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 4 OF 12 CAPLUS COPYRIGHT 2002 ACS ACCESSION NUMBER: 2000:534024 CAPLUS

DOCUMENT NUMBER:

133:276293

TITLE: Crystals of the Urokinase Type Plasminogen Activator

Variant .beta.c-uPA in Complex with Small Molecule Inhibitors Open the Way towards Structure-based Drug Design

AUTHOR(S): Zeslawska, Ewa; Schweinitz, Andrea; Karcher, Annette;

Sondermann, Peter; Sperl, Stefan; Sturzebecher, Jorg;

Jacob, Uwe

CORPORATE SOURCE: Abteilung Strukturforschung, Max-Planck-Institut fur

Biochemie, Martinsried, D-82152, Germany

SOURCE: Journal of Molecular Biology (2000), 301(2), 465-475

CODEN: JMOBAK; ISSN: 0022-2836

PUBLISHER: Academic Press DOCUMENT TYPE: Journal LANGUAGE: English

Urokinase is a serine protease involved in cancer

growth and metastasis. Here the authors present the first urokinase crystal structure in complex with reversible inhibitors at 2.1 and 2.6 .ANG. resoln. These inhibitor complex structures have been obtained from crystals of engineered urokinase type plasminogen activator designed to obtain a crystal form open for inhibitor soaking. The mutant Cl22S loses its flexible A-chain upon activation cleavage and crystallizes in the presence of benzamidine, which was later displaced by the desired inhibitor. This new soakable crystal form turned out to be of great value in the process of structure-based drug design. The evaluated binding mode of amiloride, and UKI-1D revealed a new subsite of the primary specificity pocket of urokinase that will be employed in the future ligand optimization process. (c) 2000 Academic Press.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 5 OF 12 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:441647 CAPLUS

DOCUMENT NUMBER: 133:84295

TITLE: Kunitz-type serine proteinase

inhibitors for accelerating the rate of mucociliary

clearance

INVENTOR(S): Hall, Roderick; Poll, Christopher T.; Newton, Benjamin

B.; Taylor, William J. A.

PATENT ASSIGNEE(S): Bayer Aktiengesellschaft, Germany

PCT Int. Appl., 173 pp. SOURCE:

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA:	PATENT NO.																
WO	2000037099			A.	A2 20000629			WO 1999-GB4381						1999	1222		
WO	2000037099			A.	3	2000	1026										
	W:	ΑE,	AL,	AM,	ΑT,	ΑT,	AU,	ΑZ,	BA,	BB,	BG,	BR,	BY,	CA,	CH,	CN,	CR,
		CZ,	CZ,	DE,	DE,	DK,	DK,	DM,	EE,	EE,	ES,	FI,	FI,	GB,	GD,	GE,	GH,
		GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	KR,	ΚZ,	LC,	LK,	LR,	LS,
		LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	NO,	NZ,	PL,	PT,	RO,	RU,
		SE,	SG,	SI,	SK,	SK,	SL,	ТJ,	TM,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VN,
		ZA,	ZW,	AM,	ΑZ,	BY,	KG,	ΚZ,	MD,	RU,	ТJ,	TM					
	RW:	GH,	GM,	ΚE,	LS,	MW,	SD,	SL,	SZ,	TZ,	UG,	ZW,	AT,	BE,	CH,	CY,	DE,
		DK,	ES,	FI,	FR,	GB,	GR,	ΙE,	IT,	LU,	MC,	NL,	PT,	SE,	BF,	ВJ,	CF,
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		ΙE,	SI,	LT,	LV,	FΙ,	RO										
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								1	US 1	999-	4419	66	Α	1999	1117		
								1	WO 1	999-	GB43	81	W	1999	1222		

AR The instant invention provides for a compn. and method for using Kunitz-type serine protease inhibitors, e.g., aprotinin or bikunin, for stimulating the rate of mucociliary clearance of mucus and sputum in lung airways of subjects afflicted with mucociliary dysfunctions such as cystic fibrosis.

ANSWER 6 OF 12 CAPLUS COPYRIGHT 2002 ACS ACCESSION NUMBER: 1999:669261 CAPLUS

DOCUMENT NUMBER: 132:160893

AUTHOR(S):

PUBLISHER:

TITLE: Molecular basis of specific inhibition of urokinase

plasminogen activator by amiloride Jankun, Jerzy; Skrzypczak-Jankun, Ewa

Urology Research Center, Department of Urology, Medical College of Ohio, Toledo, OH, USA CORPORATE SOURCE:

SOURCE: Cancer Biochemistry Biophysics (1999), 17(1-2),

109-123

CODEN: CABCD4; ISSN: 0305-7232 Gordon & Breach Science Publishers

DOCUMENT TYPE: Journal LANGUAGE: English

The urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA) are very similar serine proteases with the same physiol. function, the activation of plasminogen. An increased amt. or activity of uPA but not tPA has been detected in human cancers. The PAs are weak proteolytic enzymes, but they activate plasminogen to plasmin, a

strong proteolytic enzyme largely responsible for the malignant properties of cancers. It has been shown recently that the administration of uPA inhibitors can reduce tumor size. Inhibitors of uPA could therefore be used as anti-cancer and anti-angiogenesis agents. It has been found that amiloride competitively inhibits the catalytic activity of uPA but not tPA. Modification of this chem. could therefore produce a new class of uPA specific inhibitors and a new class of anti-cancer agents. The X-ray structure of the uPA complex with amiloride is not known. There are structural differences in the specificity pocket of uPA and tPA. However, the potential energy of binding amiloride is lower outside this cavity in the case of tPA. A region responsible for binding amiloride to tPA has been proposed as the loop B93-B101, reached in neg. charged amino acids present in tPA but not uPA.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 7 OF 12 CAPLUS COPYRIGHT 2002 ACS ACCESSION NUMBER: 1999:548471 CAPLUS

DOCUMENT NUMBER: 131:314149

TITLE: Organic cation transport in rabbit alveolar epithelial

cell monolayers

AUTHOR(S): Shen, Jie; Elbert, Katharina J.; Yamashita, Fumiyoshi;

Lehr, Claus-Michael; Kim, Kwang-Jin; Lee, Vincent H.

CORPORATE SOURCE: Department of Pharmaceutical Sciences, University of

Southern California, Los Angeles, CA, 90033, USA Pharmaceutical Research (1999), 16(8), 1280-1287

CODEN: PHREEB; ISSN: 0724-8741

PUBLISHER: Kluwer Academic/Plenum Publishers

DOCUMENT TYPE: Journal LANGUAGE: English

SOURCE:

Org. cation (OC) transport in primary cultured rabbit alveolar epithelial cell monolayers was characterized using [14C]-guanidine as a model substrate. Type II alveolar epithelial cells from the rabbit lung were isolated by elastase digestion and cultured on permeable filters precoated with fibronectin and collagen. Uptake and transport studies of [14C]-guanidine were conducted in cell monolayers of 5 to 6 days in culture. The cultured alveolar epithelial cell monolayers exhibited the characteristics of a tight barrier. [14C]-Guanidine uptake was temp. dependent, saturable, and inhibited by OC compds. such as amiloride, cimetidine, clonidine, procainamide, propranolol, tetraethylammonium, and verapamil. Apical guanidine uptake (Km = 129 .+-. 41 .mu.M, Vmax = 718 .+-. 72 pmol/mg protein/5 min) was kinetically different from basolateral uptake (Km = 580 .+-. 125 .mu.M, Vmax = 1,600 .+-. 160 pmol/mg protein/5 min). [14C]-Guanidine transport across the alveolar epithelial cell monolayer in the apical to basolateral direction revealed a permeability coeff. (Papp) of (7.3 .+-. 0.4) .times. 10-7 cm/s, about seven times higher than that for the paracellular marker [14C]-mannitol. Our findings are consistent with the existence of carrier-mediated OC transport in

cultured rabbit alveolar epithelial cells. THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS REFERENCE COUNT: 30 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 8 OF 12 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:85185 CAPLUS

DOCUMENT NUMBER:

TITLE:

128:228162 CASP2 molecular docking predictions with the LIGIN

software

AUTHOR(S): Sobolev, Vladimir; Moallem, Theodore M.; Wade, Rebecca

C.; Vriend, Gert; Edelman, Marvin

Department of Plant Genetics, Weizmann Institute of CORPORATE SOURCE:

Science, Rehovot, 76100, Israel

SOURCE: Proteins: Structure, Function, and Genetics (1998),

Volume Date 1997, (Suppl. 1), 210-214

CODEN: PSFGEY; ISSN: 0887-3585

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal LANGUAGE: English

Seven docking predictions were made with the LIGIN program. In six cases the location of the binding pocket was identified correctly by systematically docking everywhere within the protein structure. cases the ligand was docked to within 1.8 .ANG. RMSD of the exptl. detd. structure. LIGIN has not been optimized to deal with highly flexible ligands that dock at the surface of proteins. Consequently, in three cases the exposed part of the ligand was docked poorly, although the buried parts were docked well, and made similar at. contacts with the protein as in the exptl. detd. structure.

ANSWER 9 OF 12 CAPLUS COPYRIGHT 2002 ACS ACCESSION NUMBER: 1997:742510 CAPLUS

DOCUMENT NUMBER: 128:57249

TITLE:

Competitive inhibition of swine kidney copper amine oxidase by drugs: amiloride, clonidine, and gabexate

mesvlate

AUTHOR(S): Federico, Rodolfo; Angelini, Riccardo; Ercolini, Luca;

Venturini, Giorgio; Mattevi, Andrea; Ascenzi, Paolo

Department of Biology, Third University of Rome, Rome, CORPORATE SOURCE:

00146, Italy

Biochemical and Biophysical Research Communications SOURCE:

(1997), 240(1), 150-152

CODEN: BBRCA9; ISSN: 0006-291X

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal LANGUAGE: English

. .

Competitive inhibition of swine kidney copper amine oxidase by diuretic, antihypertensive, and anticoagulant drugs, amiloride, clonidine, and gabexate mesylate, resp., is reported. The affinity of these compds. for swine kidney copper amine oxidase is similar to that obsd. for inhibitor

binding to nitric oxide synthase and trypsin-like serine

proteinases. This finding suggests that amiloride, clonidine, and gabexate mesylate should be administrated under careful control, since enzyme cross-inhibition may occur also in vivo.

ANSWER 10 OF 12 CAPLUS COPYRIGHT 2002 ACS ACCESSION NUMBER: 1993:440959 CAPLUS

DOCUMENT NUMBER: 119:40959

TITLE: Enzyme inhibitors for treatment of periodontosis

INVENTOR(S): Imaizumi, Kazuo PATENT ASSIGNEE(S): Lion Corp, Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE ----------JP 05097708 A2 19930420 JP 1991-282090 19911002

ATPase inhibitors, cysteine or serine protease inhibitors, and/or protein kinase C inhibitors are useful for treatment of periodontosis. Acetazolamide inhibited Ca release from bone by Porphyromonas gingivalis lipopolysaccharide at ED50 of 10-4M. Acetazolamide 1, PVP 65, poly(acrylic acid) Na salt 20, PEG 10, and H2O to 100% were mixed to give a compn.

ANSWER 11 OF 12 CAPLUS COPYRIGHT 2002 ACS ACCESSION NUMBER: 1993:182795 CAPLUS

DOCUMENT NUMBER: 118:182795

TITLE: Bis(5-amidino-2-benzimidazolyl) methane and related

amidines are potent, reversible inhibitors of mast

cell tryptases

AUTHOR(S): Caughey, G. H.; Raymond, W. W.; Bacci, E.; Lombardy,

R. J.; Tidwell, R. R.

CORPORATE SOURCE: Cardiovasc. Res. Inst., Univ. California, San

Francisco, CA, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics

(1993), 264(2), 676-82

CODEN: JPETAB; ISSN: 0022-3565

DOCUMENT TYPE: Journal LANGUAGE: English

Tryptase is the major secretory protease of human mast cells and is proposed to be involved in neuropeptide processing and tissue inflammation. Exploration of the biol. of tryptase has been hindered by the lack of potent, selective inhibitors. The current study explores the properties of arom. diamidines as inhibitors of dog and human tryptase. The strongest inhibitors of tryptase in this series are bis(5-amino-2-benzimidazolyl)methane (BABIM) and (5-amidino-2benzimidazolyl)-(5-N,N'-dimethylamidino)-2-benzimidazolyl)methane, which exhibit Ki values of 1.8 and 1.4 nM, resp., in blocking the hydrolysis of tosyl-L-Gly-Pro-Lys-4-nitroanilide by human tryptase. These compds. are .apprx.10,000-fold more potent than benzamidine, and are the strongest reversible inhibitors of tryptase described to date. Other arom. monoand diamidines, including amiloride and pentamidine, are less potent. Nonetheless, they abolish tryptase activity at high inhibitor concns. The rank order of tryptase inhibitor potency parallels that of inhibitors tested against trypsin. BABIM, the only highly active member of this

series whose potency against other targets has been examd. previously, is a far stronger inhibitor of tryptase than of other trypsin-like serine proteases, including those involved with hemostasis, fibrinolysis and the complement system. Therefore, BABIM appears to have selective affinity for tryptase. In addn. to inhibiting tryptase-induced hydrolysis of peptide-based chromogenic substrates, BABIM blocks completely the reversal of vasoactive intestinal peptide-induced relaxation of isolated trachea by dog tryptase. Thus, BABIM and related amidines are potent inhibitors of mast cell tryptases that may be useful in exploring mast cell protease biol.

L3 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER:

1982:48256 CAPLUS

DOCUMENT NUMBER:

96:48256

TITLE:

Kallikrein inhibitors decrease short-circuit current

by inhibiting sodium uptake

AUTHOR (S):

Orce, Gabriel G.; Castillo, Graciela A.; Margolius,

Harry S.

CORPORATE SOURCE:

Dep. Pharmacol., Med. Univ. South Carolina,

Charleston, SC, 29425, USA

SOURCE:

Hypertension (1981), 3(6, Pt. 2), 92-5

CODEN: HPRTDN; ISSN: 0194-911X

DOCUMENT TYPE:

Journal English

LANGUAGE:

aprotinin [9087-70-1], A reversible inhibitor, and D-Phe-Phe-Arg chloromethyl ketone (DPPA) [74392-49-7], an irreversible inhibitor of kallikrein [9001-01-8] decreases short-circuit current (SCC) in the urinary bladder of the toad Bufo marinus in a dose-dependent fashion. Both agents act more rapidly and potently when added to the mucosal side of the bladder, exhibiting similar potency and effectiveness. To further define their sites of action, amphotericin B [1397-89-3] was used; this interacts with the mucosal cell membrane and increases its cation permeability, presumably by altering a barrier at the apical border that limits the rate of Na+ uptake by epithelial cells. Thus, the SCC-inhibiting effects of amiloride [2609-46-3] were reversed by mucosal amphotericin B treatment. The effects of either aprotinin or DPPA were reversed after the addn. of amphotericin B (2.0 .times. 10-5 M)to the mucosal side of the bladder. Also, when initial SCC was completely blocked by amiloride (1.0 .times. 10-4M), the addn. of amphotericin B (2.0 .times. 10-5 M) to the mucosal bath induced an amiloride-insensitive SCC, which was not affected by high concns. of either aprotinin or DPPA, but was inhibited by serosal addn. of ouabain (1.0 .times. 10-5 M). Thus, these kallikrein inhibitors act at a site along the active transport pathway that is proximal to the ouabain-sensitive site, and removal of the apical barrier by amphotericin B prevents their effect on SCC. The apical barrier appears to be a likely site of the action of these agents on SCC, suggesting a close relation between this structure and a serine proteinase involved in the uptake of Na+ by the toad bladder.